e-ISSN: 0975-5160, p-ISSN: 2820-2651

Available online on www.ijtpr.com

International Journal of Toxicological and Pharmacological Research 2023; 13(7); 202-207

Original Research Article

Intrathecal Midazolam as an Adjuvant to Bupivacaine for Spinal Anaesthesia in Orthopaedic Surgery

Pujaben A Barad[1], Kiritbhai L. Jadav[2]

[1]Assistant Professor, Department of Anaesthesia, GMERS Medical College and Hospital, Junagadh, Gujarat

[2]Assistant Professor, Department of Orthopaedics, GMERS Medical College and Hospital, Junagadh, Gujarat

Received: 30-04-2023 / Revised: 21-05-2023 / Accepted: 26-06-2023

Corresponding author: Dr. Pujaben A Barad

Conflict of interest: Nil

Abstract:

Background and Aim: The most prevalent criticism levelled against spinal anaesthesia, one of the methods used for infraumbilical procedures, is its short-lived postoperative analgesia. For extending the analgesic effect's duration, a number of adjuvants have been tested in conjunction with local anaesthetic. The goal of the current study was to determine the impact of post-operative analgesia in orthopaedic surgery using 2 mg of midazolam as an adjuvant to intrathecal bupivacaine.

Material and Methods: The study comprised 100 patients who had lower limb or hip surgeries and were either male or female, ASA grade I-II, between the ages of 20 and 50, weighing between 50 and 80 kg. Two groups of 50 patients each were created by randomly dividing the patients. Each subject received 3.6 cc of medication intravenously overall: Group 2 (BS): 3.2 ml of 0.5% hyperbaric bupivacaine + 0.4 ml of ordinary saline; Group 1 (BM): 3.2 ml of 0.5% hyperbaric bupivacaine plus 0.4 ml (2 mg) of preservative-free midazolam.

Results: The midazolam group's mean analgesia duration was longer than in the control group ($p<0.05$). Diclofenac injections used as rescue analgesics were also much less frequent in the BM group. The time it took for the BM group to reach the highest sensory level (T4) was likewise noticeably shorter. The midazolam group had a longer time to two segment regression and longer motor block duration.

Conclusion: As it extends the duration of post-operative analgesia and minimizes the need for rescue analgesia, preservative-free midazolam at a dose of 2 mg appears to be an efficient and safe adjuvant to bupivacaine in spinal anaesthesia. For more clarification, long-term analyses of the aforementioned modalities are needed in the future.

Keywords: Bupivacaine, Midazolam, Motor Block, Spinal Anaesthesia.

Introduction

One of the most adaptable regional anaesthesia methods now accessible is spinal subarachnoid block. In comparison to general anaesthesia, regional anaesthesia has a number of benefits, including a reduced stress response during surgery, a reduction in intraoperative blood loss, a decreased risk of postoperative thromboembolic events, and the provision of analgesia in the immediate postoperative period. Lower limb and lower abdomen procedures frequently use spinal anaesthetic due to its many benefits over general anaesthesia, including its quick onset, superior blockage, minimal physiological changes, low stress response, cost-effectiveness, and lower risk of postoperative morbidity.[1] Since bupivacaine has a lengthy duration of action, it has becoming more used as a spinal anaesthetic. At typical doses, it provides sufficient pain relief without causing serious adverse effects, but large doses may cause arterial hypotension as well as increased levels of sensory and motor blockage. Additionally, intravascular absorption might result in cardiac arrest, convulsions, and even death. Therefore, it was felt that the use of an adjuvant in addition to bupivacaine was necessary in order to reduce any potential side effects brought on by greater doses.

Opioids were one of many adjuvants that had been explored, but their usage is restricted due to opioid-related side effects, particularly when used neuraxially. [2] GABA, an inhibitory neurotransmitter, facilitates the inhibition of neurons, particularly those in the spinal cord. GABA receptors with motifs 1-3 and 5 are bound by and affected by benzodiazepines. A benzodiazepine derivative with a short half-life and an imidazole structure is midazolam hydrochloride.

[3] Medical professionals are familiar with the common medication midazolam for its hypnotic, anticonvulsant, anxiolytic, and sedative characteristics. [4] The effectiveness of an intrathecally given midazolam bupivacaine combination has only been studied in a small number of human trials. Midazolam has been utilised at various doses ranging from 1 mg to 6 mg, which has led to variations in the length of post-operative analgesia. As a result, there is no agreement on the precise midazolam dosage to be utilised or the length of post-operative analgesia. The goal of this study was to further evaluate the intrathecal midazolam-bupivacaine combination and see whether a small intrathecal midazolam dose could improve post-operative analgesia while reducing the risk of neurotoxicity from higher doses. The goal of the current study was to determine the impact of post-operative analgesia in orthopaedic surgery using 2 mg of midazolam as an adjuvant to intrathecal bupivacaine.

Material and Methods

The study comprised 100 patients who had lower limb or hip surgeries and were either male or female, ASA grade I-II, between the ages of 20 and 50, weighing between 50 and 80 kg. Prior to the procedure, the patients gave their valid, informed permission in writing, and the study received institutional ethical committee approval. Two groups of 50 patients each were created by randomly dividing the patients. Each subject received 3.6 cc of medication intravenously overall: Group 2 (BS): 3.2 ml of 0.5% hyperbaric bupivacaine + 0.4 ml of ordinary saline; Group 1 (BM): 3.2 ml of 0.5% hyperbaric bupivacaine plus 0.4 ml (2 mg) of preservative-free midazolam. A thorough medical history was collected, including information on current medications, previous major surgeries, and comorbid medical disorders. Exclusion criteria for the study included patients with bleeding or coagulation abnormalities, peripheral neuropathy, elevated intracranial pressure, demyelinating central nervous system disorders, spinal deformities, local sepsis, psychiatric illnesses, valvular heart diseases, a history of hypersensitivity to amide anaesthetics, and patients who were unwilling or unable to cooperate. Vital signs were collected and a thorough general physical examination was performed. Laboratory tests such as those for haemoglobin, blood sugar, renal function, and 12-lead electrocardiography were reviewed. Patients were informed of the numerical scale for rating pain. (0-10; 0 for no pain and 10 for worst pain).

Heart rate (HR), non-invasive blood pressure, a pulse oximeter, and an electrocardiogram were used to start monitoring the patients. Ringer lactate was used to initiate an intravenous (I.V.) infusion after an intravenous (I.V.) line was established with an 18-gauge cannula. In an aseptic setting, a 26 gauge Quincke needle was placed into the L3-L4 interspace while the patient was seated. Drugs were slowly injected into the subarachnoid space over the course of one to two minutes, and patients were kept supine with their heads straight. Every five minutes during the operation, the mean arterial pressure (MAP), heart rate (HR), and peripheral oxygen saturation (SpO2) were recorded. From the moment the drug was injected into the subarachnoid space until full analgesia was achieved at the level of T10, the onset of sensory block was timed. The level of sensory block obtained bilaterally was assessed using the pin-prick method, with the dermatomal level being examined every 2 minutes until the maximum level stabilised for four consecutive tests. The highest sensory level attained was registered, and assessments were carried out every 10 minutes until the block started to regress by two segments. The duration of the sensory block was calculated as the interval between the commencement of the block and the time required for two-segment regression of the block from its greatest level. During the tracking of sensory block levels following things were noted:

- The maximum sensory block level attained.
- Time to achieve this maximum sensory block level.
- Time to 2 segment regression of the sensory block from the maximum level.

Motor block

Every 2 minutes, until motor block level 2 or 3 (as measured by the Modified Bromage Scale) was reached, the onset of motor block was evaluated.

Modified bromage scale

1. No motor block
2. Inability to raise extended leg; able to move knees and feet
3. Inability to raise extended leg and move knee; able to move feet
4. Complete block of motor limb

The duration of motor block was taken as the time from complete motor block to time when lower limb can be moved.

Sedation assessment

The degree of sedation was measured with a 4-point scale:

1. no sedation,
2. light sedation,
3. moderate sedation or somnolence,
4. Deep sedation.

The period from the onset of the spinal block to the moment rescue analgesia was administered (when

pain exceeded a numerical rating of 5 or upon patient demand) was used to calculate the duration of analgesia. Diclofenac (aqueous) 75 mg was administered intravenously to treat post-operative discomfort. The total number of dosages used was noted. If there was any hypotension (mean B.P. 65 mm of hg), it was treated with a fluid bolus administered intravenously and increasing doses of the vasopressor drug mephentermine (6 mg). After surgery, any adverse effects such as nausea, vomiting, shivering, or others were monitored for 24 hours and treated accordingly.

Statistical analysis

The collected data was organised, inputted, and exported to the data editor page of SPSS version 15 (SPSS Inc., Chicago, Illinois, USA) after being combined and entered into a spreadsheet programme (Microsoft Excel 2007). The level of significance and confidence level for each test were set at 5% and 95%, respectively.

Results

Regarding age, weight, sex distribution, and ASA physical state, both groups were comparable. The mean time for the commencement of sensory level in both the study (BM) and control (BS) groups did not statistically differ significantly. When compared to controls, patients in the BM group took less time on average to reach their maximum sensory level. It was determined that there was a statistically significant difference between the two groups (p 0.05). Only one-third (34%) of patients in the control group were able to reach the maximal sensory T4 level, compared to nearly half (46%) of patients in the BM group. Patients in the midazolam group took longer than patients in the control group to regress to the two segment level from the highest sensory level reached. It was determined that the difference was statistically significant.

Both groups experienced motor block at about the same average time. There was no statistically significant change (p>.05). In the midazolam group compared to the controls, it was discovered that the mean duration of motor block was longer. This finding was statistically significant. In the midazolam group compared to the controls, it was discovered that the mean duration of motor block was longer. This finding was statistically significant (p 0.05), indicating that midazolam prolonged the motor block significantly. In the BM group, the mean analgesia duration was 430.25 + 60.64 minutes, compared to 251.9 + 41.10 minutes in the control group. The results of the t-test revealed that the values were statistically very significant (p 0.05). These results imply that intrathecal midazolam greatly lengthens the analgesic effect.

The duration of post-operative analgesia was significantly prolonged in the midazolam group's patients. Additionally, they required less rescue analgesia than the control group, and this difference was determined to be statistically significant. Patients in both groups were equivalent since they did not receive any sedation prior to surgery (sedation score of 1). The intra-operative sedation score was recorded 30 minutes after the surgery began. 63% of patients in the midazolam group had a sedation level of 2, and the remaining 37% had a sedation score of 3. In contrast, 67% of patients in the control group had a sedation level of 1 and 33% had a sedation score of 2. A statistical comparison revealed that the intra-operative sedation score was statistically highly significant (p 0.05), suggesting that midazolam, when administered intrathecally, also produces sedation, which may lessen anxiety and improve patient comfort while reducing the need for intravenous sedatives.

Only 7% of patients in the midazolam group had minor sedation (sedation score 2) after surgery. The other patients were not sedated after surgery. It was not determined that the difference was statistically significant.

Mean arterial pressure (MAP), heart rate (HR), and oxygen saturation (SpO2) values were obtained every five minutes until the surgery was finished in both groups. In both groups, the mean values of HR and SpO2 were discovered to be comparable and statistically insignificant. The difference between the mean MAP at the beginning of surgery and the first 30 minutes of operation was not statistically significant. At 35 and 40 minutes after surgery, patients in the midazolam group experienced a substantial decline in mean arterial pressure (p 0.05). Other values that were comparable between the groups and statistically insignificant were discovered. Episodes of hypotension occurred in 13% of individuals in group BM and 47% of participants in group BS. When comparing the two groups statistically, a significant difference was discovered (p 0.05). No patients in the study group or the control group experienced any episodes of bradycardia, shivering, nausea, or respiratory depression.

Table 1: Demographic Distribution of Study Participants

Variables	Group 1 (n=50) Mean±SD	Group 2 (n=50) Mean±SD	P value
Age (years)	37.40±8.22	35.95±10.20	0.35
Weight (kg)	61.9±6.32	62.1±8.48	0.5

Statistically significance at p≤0.05

Table 2: Clinical parameters among Study Participants

Variables	Group 1 (n=50)	Group 2 (n=50)	P value
Onset(min)	2.20+0.70	2.35+0.68	0.7
Time to maximum level (min)	9.15+3.10	10.32+2.11	0.03*
Maximum sensory level assessment			
T4 Count (%)	23 (46)	17 (34)	0.05*
T5 Count (%)	11 (22)	17 (34)	
T6 Count (%)	16 (32)	13 (26)	
T7 Count (%)	0	3 (6)	
Time (min.) to two segment regression	136.50+25.78	114.05+21.19	0.01*
Duration of Analgesia (min.)	430.25+60.64	251.9+41.10	0.01*
Rescue analgesia(No. of Inj. Diclofenac)	1.92±0.59	3.1±1.2	0.001*
Motor block (min.)			
Onset	3.70+1.23	3.78+1.09	0.98
Duration	210.1+22.90	188.8+22.54	0.002*

* indicates statistically significance at p≤0.05

Discussion

Midazolam given intravenously or epidurally in humans modifies the spinal nociceptive response in a dose-dependent manner. Numerous researchers have attempted to investigate the mechanism of midazolam's analgesic properties. [5-7] the results of the current study demonstrated that patients who received intrathecal midazolam along with bupivacaine experienced significantly longer analgesia than those who received only intrathecal bupivacaine. Several earlier investigations on the subject of analgesia duration came to similar conclusions. [1,8] Higher drug doses were likely employed in the Abd El Aziz1 trial than in our investigation, which resulted in a significantly longer duration of analgesia, although Gupta et al.[9] concluded that 2.5 mg of midazolam produced a similar prolongation to 2.0 mg of midazolam. When compared to low dose clonidine, intrathecal midazolam was also observed to increase the length of postoperative analgesia (p0.05).10 Similar results were shown by Chattopadhyay et al.[11], although they did not demonstrate the same degree of extension of analgesia as we did, most likely because we used lower dosages of bupivacaine. The dose-dependent analgesic effects of intrathecal midazolam were further established by Kim et al.[12] When 2 mg of midazolam was administered as opposed to 1 mg, which was greater when compared to those getting only bupivacaine, the duration of analgesia was prolonged for a longer period of time. Compared to our trial, this study showed a less pronounced increase in the duration of analgesia, which can be explained by the use of a lower dose of bupivacaine (1ml) and a different scale for measuring pain. There aren't many clinical research that have examined the effectiveness of midazolam as a supplement to nerve blocks when used as an adjuvant to LA because earlier studies revealed the drug's in vitro neurotoxicity and meagre efficacy. [13,14] However, Dittmar et al.[15] used astrocyte-conditioned human umbilical vein endothelial cells as an in vitro model to investigate the degree of apoptosis and found that midazolam did not significantly change markers of apoptosis in contrast to control. Ulbrich et al. [16] evaluated the mitochondrial membrane potential of damaged neuronal cells using an experimental process before subjecting them to various LA additions. They discovered that midazolam was unable to either protect or worsen these damaged neurons. While Batra et al. [17] observed a prolonging of analgesia in their trial, the effective duration was different from our study. This study focused on individuals who underwent knee arthroscopy, a very painless technique that typically results in less post-operative discomfort for patients. In pregnancy-induced hypertension patients undergoing an elective caesarean surgery, Dodawad et al. [18] similarly noted a substantial lengthening in the time spent in analgesia in the midazolam group.

The midazolam group required much less rescue analgesia than the controls did. Similar findings were obtained by Gupta et al. in terms of the dosage of additional analgesics that was necessary. [9] Results of our study agreed with those of Prakash et al. They discovered that the midazolam group had much lower supplemental analgesic needs when using diclofenac. (p< .001). [19] T4 was the highest sensory level attained in the midazolam and control groups. Maximum sensory level was reached far more quickly in the midazolam group, and there was a statistically significant difference between the two groups. On this criterion, other studies produced conflicting findings. Joshi et al. discovered that the midazolam group took noticeably shorter time to reach their highest sensory level (p value 0.05). [10] Dodawad et al. also noted that the midazolam group reached

the maximal sensory level more sooner than the controls did.18 In the current investigation, the midazolam group showed a significantly longer duration to two segment regression of sensory analgesia than the controls. Batra et al. reached similar conclusions, showing that the study group's time to two-segment analgesia regression was greater than that of the control group. ($p<0.05$)[17] In this investigation, intrathecal midazolam significantly lengthened the motor block period (p 0.001). Similar findings were made by Bharti et al, who discovered that the midazolam group's motor block lasted longer than the control group's did ($p=0.01$).20 Chattopadhyay et al. noted similar results in terms of the lengthening of the duration of the motor block. ($p<0.05$)[11] High levels of sedation in the midazolam group demonstrated that midazolam also has sedative effects when administered intra-thecally. This is advantageous since it eliminates the need for intravenous sedation. The patient is kept calm, which may improve their capacity to tolerate the length of surgery and improve their recovery. The first 30 minutes of the operation's mean MAP levels were statistically comparable and not significant. The stronger anxiolytic effect of intrathecal midazolam, which manifests mostly after 30 minutes after surgery, may be the cause of the midazolam group's lower MAP readings at 35 minutes and 40 minutes compared to controls. Heart rate and SPO2 values were discovered to be similar between the two groups. Numerous other investigations similarly failed to detect any appreciable variation in haemodynamic factors like heart rate and blood pressure. [9-12,15-18] Compared to patients in the control group, study group patients experienced considerably fewer bouts of hypotension. This agrees with the findings of Joshi et al. [10] much earlier research did not uncover anything like this. [8-10, 15-17] More studies need to be done to assess this parameter with more number of patients. The relatively small sample size, single-center design, brief operation period, and use of a set dose of midazolam were all limitations of this study. Therefore, to determine the most effective midazolam dose and to confirm or refute the findings of the present investigation, bigger, multicenter studies with a larger sample size and longer operations should be done.

Conclusion

As it extends the duration of post-operative analgesia and minimises the need for rescue analgesia, preservative-free midazolam at a dose of 2 mg appears to be an efficient and safe adjuvant to bupivacaine in spinal anaesthesia. For more clarification, long-term analyses of the aforementioned modalities are needed in the future.

References

1. Aziz ME. Evaluation of intrathecal midazolam as adjuvant to bupivacaine 0.5% for spinal anaesthesia in orthopedic surgery. Ain Shams J Anesthesiol. 2009; 2:31–4.
2. Swain A, Nag DS, Sahu S, Samaddar DP. Adjuvants to local anaesthetics: Current understanding and future trends. World J Clin Cases 2017; 5:307–23.
3. Lewter LA, Golani LK, Cook JM, Li JX. Blockade of α1 subtype GABAA receptors attenuates the development of tolerance to the antinociceptive effects of midazolam in rats. Behav Pharmacol 2021; 32:345–50.
4. Maheshwari M, Sanwatsarkar S, Katakwar M. Pharmacology related to paediatric anaesthesia. Indian J Anaesth 2019;63: 698-706.
5. Goodchild CS, Noble J. The effects of intrathecal midazolam on sympathetic nervous system reflexes in man-a pilot study. Br J Clin Pharmacol. 1987;23(3):279–85.
6. Faull RL, Villiger JW. Benzodiazepine receptors in the human spinal cord: a detailed anatomical and pharmacological study. Neuroscience. 1986;17(3):791–802.
7. Muller H, Gerlach H, Boldt H. Spasticity treatment with spinal morphine or midazolam: in vitro experiments, animal studies and clinical studies on compatibility and effectiveness. Anaesthesist. 1986;35(5):306–16.
8. Prathasarathy S. The effect of addition of intrathecal midazolam 1.5 mg to bupivacaine in patients undergoing abdominal hysterectomy. SriLankan J Anaesthesiol. 2011;19(2):81–5.
9. Gupta A, Prakash S, Deshpande S, Kale KS. The effect of intrathecal midazolam 2.5 mg with bupivacaine on postoperative pain relief in patients undergoing orthopaedic surgery. Internet J Anesthesiol. 2007;14(2):1–4.
10. Joshi SA, Khadke VV, Subhedar RD, Patil AW, Motghare VM. Comparative evaluation of intrathecal midazolam and low dose clonidine: efficacy, safety and duration of analgesia. A randomized, double blind, prospective clinical trial. Indian J Pharmacol. 2012; 44(3):357–61.
11. Chattopadhyay A, Maitra S, Sen S, Bhattacharjee S, Layek A, Pal S. A study to compare the analgesic efficacy of intrathecal bupivacaine alone with intrathecal bupivacaine- midazolam combination in patients undergoing elective infraumbilical surgery. Anesthesiol Res Pract. 2013; 2013:567134.
12. Kim MH, Lee YM. Intrathecal midazolam increases the analgesic effects of spinal

blockade with bupivacaine in patients undergoing haemorrhoidectomy. Br J Anaesth. 2001; 86(1):77–9.
13. Ponde VC. Recent developments in paediatric neuraxial blocks. Indian J Anaesth 2012; 56:470-8.
14. Bailard NS, Ortiz J, Flores RA. Additives to local anaesthetics for peripheral nerve blocks: Evidence, limitations, and recommendations. Am J Health Syst Pharm 2014; 71:373–85?
15. Dittmar MS, Petermichl W, Lindner R, Sinner B, Graf BM, Schlachetzki F, et al. In vitro induction of endothelial apoptosis of the post-hypoxic blood-brain barrier by isoflurane but not by sevoflurane and midazolam. PLoS One 2015;10:e0130408
16. Ulbrich F, Eisert L, Buerkle H, Goebel U, Schallner N. Propofol, but not ketamine or midazolam, exerts neuroprotection after ischaemic injury by inhibition of Toll-like receptor 4 and nuclear factor kappa-light-chain-enhancer of activated B-cell signalling: A combined in vitro and animal study. Eur J Anaesthesiol 2016; 33:670–80.
17. Batra YK, Jain K, Chari P, Dhillon MS, Shaheen B, Reddy GM. Addition of intrathecal midazolam to bupivacaine produces better post-operative analgesia without prolonging recovery. Int J Clin Pharmacol Ther. 1999; 37(10):519–23.
18. Dodawad R, Sumalatha G, Pandarpurkar S, Jajee P. Intrathecal Midazolam as an adjuvant in pregnancy induced hypertensive patients undergoing an elective caesarean section: A clinical comparative study. Anesthesiol Pain Med. 2016; 6(5):1–7.
19. Prakash S, Joshi N, Gogia AR, Prakash S, Singh R. Analgesic efficacy of two doses of intrathecal midazolam with bupivacaine in patients undergoing cesarean delivery. Reg Anesth Pain Med. 2006; 31(3):221– 6.
20. Bharti N, Madan R, Mohanty PR, Kaul HL. Intrathecal midazolam added to bupivacaine improves the duration and quality of spinal anaesthesia. Acta Anaesthesiol Scand. 2003; 47(9):1101–5.